09/576944

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| APPLICATION NUMBER | FILING DATE | FIRST NAMED APPLICANT | ATTY. DOCKET NO. |
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EXAMINER: GAMBEL, [illegible]

| ART UNIT | PAPER NUMBER |
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| 1644 | 6 |

DATE MAILED: 10/03/01

HM22/1003

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

## OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 7/23/01

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☑ Claim(s) 1-21 is/are pending in the application.
Of the above, claim(s) 1-10, 15-21 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 11-14 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☑ Notice of Reference Cited, PTO-892
☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☑ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

## DETAILED ACTION

1. Applicant's election of Group II (claims 11-14) and the species B (anti-CD40L antibodies) in Paper No. 5 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

With respect to applicant traversal on the species of anti-CD40 antibodies, anti-CD40L antibodies, CD40-Ig and CD40L-Ig that no serious burden is placed on the examiner; MPEP 803 states that the Inventions be either independent or distinct and a burden on the Examiner if restriction is required. For the reasons of record, the structures of these costimulation blockade agents are distinct.

Claims 1-10 and 15-21 are withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention and species. The examiner appreciates applicant's recognition that claim 10 belonged to Group I only. However, it is noted that the preamble of claim 11 recites "the method of claim 11" wherein claim 11 is a composition.

2. Applicant's IDS, filed 10/5/98 (Paper No. 5), is acknowledged.

Applicant is required to provide the date and page numbers for Reference #AZ3; Wiederrecht et al., Ann. NY Acad. Sci.

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention.

4. Formal drawings, filed 5/18/98, comply with 37 CFR 1.84.
Please see the enclosed form PTO-948.

5. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate corrections are required

6. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 11, 12 and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "costimulation blockade agents and biologically derivatives" consisting of those specific agents set forth in claim 13 and disclosed in the specification as filed, does not reasonably provide enablement for any "costimulation blockade agent and biologically derivative thereof". The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies such "agents" and "derivatives" other than those encompassed by the specific agents set forth in claim 13. While "costimulation blockade agents and biologically derivatives" may have some notion of the activity of the "agents" and "derivatives", claiming biochemical molecules by such properties fails to provide sufficient guidance and direction as to how the skilled artisan can make and use such "agents" and "derivatives", commensurate in scope with the claimed invention. It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions can result in substantially different pharmacological activities. Applicant has not enabled structurally related and unrelated compounds comprising "any substance which inhibits costimulation" (page 9, paragraph 6 of the specification) or "any agent that has been modified" (page 14, paragraph 3 of the specification) would be expected to have greater differences in their activities. There is insufficient direction or objective evidence as to how to make and to how to use any agent which blocks any costimulatory activity (e.g. desired/intended effect of the claimed limitations) for the number of possibilities associated with the myriad of direct and indirect effects associated with various costimulatory pathways or molecules and, in turn, as to whether such a desired effect can be achieved or predicted, as encompassed by the claims.

Harlan states that whether you go humanized antibody, peptide, soluble receptor, or saccharide; it's still a long way to product (Edgington, Biotechnology 10: 383-389, 1992; see entire document, particularly page 386, column 3, paragraph 4).

Applicant is relying upon certain biological activities and the disclosure of a limited representative number of species to support an entire genus. It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biology, expression and pharmacology of receptors and ligands. Therefore, structurally unrelated "costimulation blockade agents" encompassed by the claimed invention other than "those set forth in claim 13" would be expected to have greater differences in their activities. For example, it is noted that antibodies and soluble receptors do not share critical common structural attributes, as antibodies and soluble proteins differ in structure and physicochemical properties.

Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality (e.g. ligand or receptor) requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence and in turn utilizing predicted structural determinations to ascertain binding or functional aspects ligands and receptors and finally what changes can be tolerated with respect thereto is complex and well outside the realm of routine experimentation. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. . Because of the lack of sufficient guidance and predictability in determining which structures would lead to desired "costimulation blockade agents" with the desired properties and that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.); it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of "costimulation blockade agents" encompassed by the claimed invention.

Skolnick et al. (Trends in Biotech., 18(1):34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2). In the absence of sufficient guidance and direction to the structural and functional analysis, applicant's reliance upon certain species does not appear to provide sufficient enabling support for any costimulation blockade agent and so the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

For example, Lederman et al. (Molecular Immunology 28: 1171-1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document).

For example, Li et al. (PNAS 77: 3211-3214, 1980) disclose that dissociation of immunoreactivity from other biological activities when constructing analogs (see entire document).

"It is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

Without sufficient guidance, making and using ligands and CD28 receptors would have been unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, the changes which can be made in the structure of any "costimulation blockade agent" or "biologically derivative thereof" and still provide or maintain sufficient or the claimed activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue

Applicant should limit the "costimulatory blockade agents" and "derivatives" to those set forth in claim 13 and in the specification as filed to obviate this rejection.

8. Claim 13 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 13 is indefinite in its preamble of "the method of claims 11" because claim 11 and, in turn, claim 13 is drawn to a "composition" and not a "method".

B) Claims 11-13 are indefinite in that the antecedent basis for "a biologically active derivative thereof" is unclear (e.g. agent or rapamycin).

C) Applicant should specifically point out the support for any amendments made to the disclosure. See MPEP 714.02 and 2163.06

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

11. Although the claims are drawn to the elected species if CD40L-specific antibodies, the following art rejections of record in parent application USSN 09/075,311 are set forth herein in the interest of compact prosecution, given the broad recitation of claimed compositions

12. Claims 11, 13 and 14 are rejected under 35 U.S.C. § 102(e) as being anticipated by de Boer et al. (U.S. Patent No. 5,869,050) (1449). De Boer et al. teaches compositions comprising at least B7-specific antibodies (and modified forms thereof) and immunosuppressive agents comprising rapamycin as well as formulations including oils (see entire document, including Detailed Description of the Invention, particularly columns 5-8). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced antibodies and immunosuppressive agents. Although, the term "kit" is not specifically taught by the reference.

13. Claims 11, 13 and 14 are rejected under 35 U.S.C. § 102(e) as being anticipated by de Boer et al. (U.S. Patent No. 5,747,034) (1449). De Boer et al. teaches compositions comprising at least B7-specific antibodies (and modified forms thereof) and immunosuppressive agents comprising rapamycin as well as formulations including oils (see entire document, including Detailed Description of the Invention, and Compositions Including Immunosuppressive Agents and Formulations and Methods of Administration, columns 14-16). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced antibodies and immunosuppressive agents. For examination purposes, the term "kit" is interpreted to mean "composition" or "formulation" and read on the active or essential ingredients of the "composition/formulation/kit (i.e. B7-specific antibodies and rapamycin.

14. Claims 11-14 are rejected under 35 U.S.C. § 103(a) as being unpatentable over de Boer et al. (U.S. Patent No. 5,869,050) (1449) AND/OR de Boer et al. (U.S. Patent No. 5,747,034) (1449) in view of Kelly et al. (U.S. Patent No. 5,118,493) (1449).

de Boer et al. ('050) and de Boer et al. ('034) are taught above and differ from the claimed compositions by not disclosing the use of fish oils as the type of oil suitable for the compositions or formulations taught for immunosuppression.

Kelly et al. teach the use of fish oils for immunosuppressive agents such as cyclosporin (see entire document).

Given the reduced nephrotoxicity associated with fish oils with immunosuppressive agents as taught by Kelly et al.; one of ordinary skill in the art at the time the invention was made would have been motivated to select such fish oils as a suitable oil for immunosuppressive compositions and formulations as taught by de Boer et al.. in immunosuppressive regimens.

While the claim recites a kit, no positive recitation of the ingredients distinguishes it over the references; therefore the kit is encompassed by the references. However, if this is not the case, it is a well known convention in the art to place these components in a kit for convenience and economy.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. The following rejections are applicable as they read on the elected species of anti-CD40L antibodies.

16. Claims 11, 13 and 14 are rejected under 35 U.S.C. § 102(e) as being anticipated by Chen et al. (U.S. Patent No. 5,990,109). Chen et al. teaches compositions comprising at least CD40L-specific antibodies and immunosuppressive agents comprising rapamycin (see entire document, including Detailed Description of the Invention, particularly column 21, paragraphs 1-3 and claims 37-38). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced antibodies and immunosuppressive agents. Although, the term "kit" is not specifically taught by the reference, there is no recitation that separates the prior art compositions comprising the same active ingredients as the instant claims.

17. Claims 11, 13 and 14 are rejected under 35 U.S.C. § 102(e) as being anticipated by Nadler et al. (U.S. Patent No. 5,962,415). Nadler et al. teaches compositions comprising at least CD40L-specific antibodies and immunosuppressive agents comprising rapamycin (see entire document, including Detailed Description of the Invention, particularly column 8, paragraphs 1-3). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced antibodies and immunosuppressive agents. Although, the term "kit" is not specifically taught by the reference, there is no recitation that separates the prior art compostions comprising the same active ingredients as the instant claims.

18. Claims 11-14 are rejected under 35 U.S.C. § 103(a) as being unpatentable over de Noelle et al. (U.S. Patent No. 5,942,229) in view of Chen et al. (U.S. Patent No. 5,990,109) AND/OR Nadler et al. (U.S. Patent No. 5,962,415) and further in view of Kelly et al. (U.S. Patent No. 5,118,493) (1449).

Noelle et al. teach the coadministration of two immunosuppressive agents comprising CD40L-specific antibodies (see columns 10-11, Section V) as well as art known compositions (see columns 8-10, Section IV.)and immunosuppressants (see entire document).

Noelle et al. differs from the claimed invention by teaching art known immunosuppressant rapamycin per se and by not disclosing the use of fish oils as the type of oil suitable for the compositions or formulations taught for immunosuppression.

Chen et al. teach compositions comprising at least CD40L-specific antibodies and immunosuppressive agents comprising rapamycin (see entire document, including Detailed Description of the Invention, particularly column 21, paragraphs 1-3 and claims 37-38).

Nadler et al. (U.S. Patent No. 5,962,415). Nadler et al. teach compositions comprising at least CD40L-specific antibodies and immunosuppressive agents comprising rapamycin (see entire document, including Detailed Description of the Invention, particularly column 8, paragraphs 1-3).

In contradistinction with Chen et al. and Nadler et al., Noelle et al. provides the expectation of success and motivation that CD40L-specific antibodies was a key ingredient of immunosuppressive formulations.

Kelly et al. teach the use of fish oils for immunosuppressive agents such as cyclosporin (see entire document).

Given the reduced nephrotoxicity associated with fish oils with immunosuppressive agents as taught by Kelly et al.; one of ordinary skill in the art at the time the invention was made would have been motivated to select such fish oils as a suitable oil for immunosuppressive compositions and formulations as taught by de Noelle et al., Chen et al. and Nadler et al. in immunosuppressive regimens.

While the claim recites a kit, no positive recitation of the ingredients distinguishes it over the references; therefore the kit is encompassed by the references. However, if this is not the case, it is a well known convention in the art to place these components in a kit for convenience and economy.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Phillip Gambel, PhD.
Patent Examiner
Technology Center 1600
October 1, 2001